The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000546.6(TP53):c.733G>A (p.Gly245Ser)

Version: 1.1

CA000367

12365 (ClinVar)

Gene: TP53 (HGNC:7157)
Condition: Li-Fraumeni syndrome (MONDO:0018875)
Inheritance Mode: Autosomal dominant inheritance
UUID: ed201831-1d8d-4c6d-ad13-1055f8d3407b
Approved on: 2024/8/5
Published on: 2024/8/5

HGVS expressions

NM_000546.6(TP53):c.733G>A (p.Gly245Ser)
NM_000546.6:c.733G>A
NC_000017.11:g.7674230C>T
CM000679.2:g.7674230C>T
NC_000017.10:g.7577548C>T
CM000679.1:g.7577548C>T
NC_000017.9:g.7518273C>T
NG_017013.2:g.18321G>A
ENST00000503591.2:c.733G>A
ENST00000508793.6:c.733G>A
ENST00000509690.6:c.337G>A
ENST00000514944.6:c.454G>A
ENST00000604348.6:c.712G>A
ENST00000269305.9:c.733G>A
ENST00000269305.8:c.733G>A
ENST00000359597.8:c.733G>A
ENST00000413465.6:c.733G>A
ENST00000420246.6:c.733G>A
ENST00000445888.6:c.733G>A
ENST00000455263.6:c.733G>A
ENST00000504290.5:c.337G>A
ENST00000504937.5:c.337G>A
ENST00000509690.5:c.337G>A
ENST00000510385.5:c.337G>A
ENST00000514944.5:c.454G>A
ENST00000610292.4:c.616G>A
ENST00000610538.4:c.616G>A
ENST00000610623.4:c.256G>A
ENST00000615910.4:c.700G>A
ENST00000617185.4:c.733G>A
ENST00000618944.4:c.256G>A
ENST00000619186.4:c.256G>A
ENST00000619485.4:c.616G>A
ENST00000620739.4:c.616G>A
ENST00000622645.4:c.616G>A
ENST00000635293.1:c.616G>A
NM_000546.5:c.733G>A

NM_001126112.2:c.733G>A
NM_001126113.2:c.733G>A
NM_001126114.2:c.733G>A
NM_001126115.1:c.337G>A
NM_001126116.1:c.337G>A
NM_001126117.1:c.337G>A
NM_001126118.1:c.616G>A
NM_001276695.1:c.616G>A
NM_001276696.1:c.616G>A
NM_001276697.1:c.256G>A
NM_001276698.1:c.256G>A
NM_001276699.1:c.256G>A
NM_001276760.1:c.616G>A
NM_001276761.1:c.616G>A
NM_001276695.2:c.616G>A
NM_001276696.2:c.616G>A
NM_001276697.2:c.256G>A
NM_001276698.2:c.256G>A
NM_001276699.2:c.256G>A
NM_001276760.2:c.616G>A
NM_001276761.2:c.616G>A
NM_001126112.3:c.733G>A
NM_001126113.3:c.733G>A
NM_001126114.3:c.733G>A
NM_001126115.2:c.337G>A
NM_001126116.2:c.337G>A
NM_001126117.2:c.337G>A
NM_001126118.2:c.616G>A
NM_001276695.3:c.616G>A
NM_001276696.3:c.616G>A
NM_001276697.3:c.256G>A
NM_001276698.3:c.256G>A
NM_001276699.3:c.256G>A
NM_001276760.3:c.616G>A
NM_001276761.3:c.616G>A

Pathogenic

Met criteria codes 7

PS2_Moderate PM1 PM2_Supporting PP4_Moderate PS3 PS4 PP3

Not Met criteria codes 10

BA1 PM5 BS2 BS1 BS4 BS3 BP4 PVS1 PS1 PP1

Evidence Links 0

Expert Panel

TP53 VCEP

Criteria Specification Information

Criteria Specification: *ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

TP53 VCEP

The NM_000546.6: c.733G>A variant in TP53 is a missense variant predicted to cause substitution of glycine by serine at amino acid 245 (p.Gly245Ser). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; Internal lab contributor: SCV000184981.8). This variant has been reported in an additional individual meeting Classical criteria and 11 individuals meeting Revised Chompret criteria. Based on this evidence, this variant scores 8 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs: 11370630, 32156018, 32888145, 33245408, 34670578, 35974385, 20522432, 24122735, Internal lab contributor: SCV000184981.8). At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributors: SCV000184981.8). This variant has an allele frequency of 0.000002543 (3/1179926 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PMIDs: 12826609, 30224644, 29979965) (PS3). This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PMID: 8023157) (PM1). Computational predictor scores (BayesDel = 0.5536; Align GVGD = Class C55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3). In summary, this variant meets the criteria to be classified as Pathogenic for Li Fraumeni Syndrome based on the ACMG/AMP criteria applied, as specified by the ClinGen TP53 VCEP: PS2_Moderate, PS4_Very Strong, PP4_Moderate, PM2_Supporting, PS3, PM1, PP3. (Bayesian Points: 20; VCEP specifications version 2.0; 7/24/2024)

Met criteria codes

PS2_Moderate	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual with a strongly LFS-associated cancer totaling 2 phenotype points (PS2_Moderate; Internal lab contributor: SCV000184981.8).
PM1	✔	This variant resides within a codon (NM_00546.4: 175, 245, 248, 249, 273, 282) of TP53 that is defined as a mutational hotspot by the ClinGen TP53 VCEP (PMID: 8023157) (PM1).
PM2_Supporting	✔	This variant has an allele frequency of 0.000002543 (3/1179926 alleles) in the European (non-Finnish) population in gnomAD v4.1.0 which is lower than the Clingen TP53 VCEP threshold (<0.00004) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PP4_Moderate	✔	At least two individuals with this variant were found to have a variant allele fraction of 5-25%, which is a significant predictor of variant pathogenicity (PP4_Moderate, PMID: 34906512, Internal lab contributors: SCV000184981.8).
PS3	✔	In vitro assays performed in yeast and/or human cell lines showed non-functional transactivation and loss of growth suppression activity indicating that this variant impacts protein function (PMIDs: 12826609, 30224644, 29979965) (PS3).
PS4	✔	PS4_VERY STRONG APPLIED This variant has been reported in 1 individual meeting Classical criteria and 11 individuals meeting Revised Chompret criteria. Based on this evidence, this variant scores 8 total points meeting the TP53 VCEP phenotype scoring criteria of ≥ 8 points. (PS4_Very Strong; PMIDs: 11370630, 32156018, 32888145, 33245408, 34670578, 35974385, 20522432, 24122735, Internal lab contributor: SCV000184981.8).
PP3	✔	Computational predictor scores (BayesDel = 0.5536; Align GVGD = Class C55) are above recommended thresholds (BayesDel > 0.16 and an Align GVGD Class of > 15), evidence that correlates with impact to TP53 via protein change (PP3).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	Two different missense variants (c.733G>C, c.733G>T) in the same codon have been reported (ClinVar IDs 376604, 12349). However, the variants have not yet been curated to determine if they would be classified as pathogenic or likely pathogenic by the ClinGen TP53 VCEP's specifications (PM5 not evaluated).
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000546.6(TP53):c.733G>A (p.Gly2…	Pathogenic	Li-Fraumeni Syndrome	2024-08-05	1.1	ClinGen TP53 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for TP53 Version 2.0.0	TP53
View		Pathogenic	Li-Fraumeni Syndrome	2020-01-24	1.0	-	TP53

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